TRANSMITTAL OF APPEAL BRIEF (Small Entity)

Docket No.
MSU 4.1-528

In Re Application Of: **Linda S. Mansfield, Mary G. Rossano, Alice J. Murphy and Ruth A. Vrable**

Application No.	Filing Date	Examiner	Customer No.	Group Art Unit	Confirmation No.
09/669,833	September 26, 2000	Padmavathi Baskar	21036	1645	2531

Invention: **VACCINE TO CONTROL EQUINE PROTOZOAL MYELOENCEPHALITIS IN HORSES**

COMMISSIONER FOR PATENTS:

Transmitted herewith in triplicate is the Appeal Brief in this application, with respect to the Notice of Appeal filed on:
May 5, 2005

☒ Applicant claims small entity status. See 37 CFR 1.27

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Signature

Dated: July 1, 2005

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I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)] on July 1, 2005.
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appl. No. : 09/669,833 Confirmation No. 2531

Applicants : Linda S. Mansfield, Mary G. Rossano, Alice J. Murphy, and Ruth A. Vrable

Filed : September 26, 2000

Title: VACCINE TO CONTROL EQUINE PROTOZOAL MYELOENCEPHALITIS IN HORSES

TC/A.U. : 1645

Examiner : Padmavathi Baskar, Ph.D.

Docket No. : MSU 4.1-528

Customer No. : 21036

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BRIEF UNDER 37 C.F.R. § 41.37

Sir:

This is an appeal from a final rejection in the above entitled application. The claims on appeal are set forth as Claims Appendix. An oral hearing will be requested. Enclosed is the fee due upon filing of the Brief.

(1) Real Party in Interest

The real party in interest is the Board of Trustees operating Michigan State University, East Lansing, Michigan, a constitutional corporation of the State of Michigan, which is the assignee of the above entitled application.

(2) Related Appeals and Interferences

The present application is a divisional application of Application Serial No. 09/513,086 ('086), filed February 24, 2000, and which claims benefit of a provisional patent Application No. 60/152,193, filed September 2, 1999. The '086 application relates to a vaccine comprising the 16 and 30 kDa antigens.

This application is related to Application Serial No. 09/669,843 ('843) which relates to a monoclonal antibody which selectively binds to a *Sarcocystis neurona* antigen; Application Serial No. 09/670,096 ('096), relating to compositions and method for treating an equid infected with *Sarcocystis neurona* with antibodies against the 16 ±4 and 30 ±4 kDa antigens; Application Serial No. 09/670,244 ('224)

which relates to recombinant protein comprising the 16 ±4 and 30 ±4 kDa antigens; and Application Serial No. 09/670,355 ('355), relating to a vaccine comprising DNA encoding the 16 ±4 and 30 ±4 kDa antigens. The above applications were all filed on September 26, 2000.

The '355 application and the '244 application have been abandoned. Application Serial No. 09/670,096 ('096) is on appeal. No application has been allowed. There are no other related appeals and interferences.

(3) Status of Claims

Claims 29 and 30 are pending in the application. Claims 29 and 30 were rejected. No claims have been allowed.

(4) Status of Amendments

An Amendment under 37 C.F.R. 1.116 was mailed on February 24, 2005. In the Amendment Claim 30 was cancelled. Claim 29 was amended to correct formal errors in sections (d) and (e). The amendment was entered.

(5) Summary of Claimed Subject Matter

The claimed subject matter in Claim 29 is a method for producing an antibody for use as a passive immunity vaccine in horses against a *Sarcocystis neurona* antigen selected from the group consisting of a 16 (+/-4) kDa antigen and a 30 (+/-4) kDa antigen, as determined by SDS polyacrylamide gel electrophoresis comprising:

(Support for this is found at page 5, lines 13-24; page 7, lines 21-30; page 10, lines 30-34; page 12, lines 31-35; page 15, lines 18-21; page 26, lines 20-26 of the specification.)

(a) providing a *Sarcocystis neurona* antigen selected from the group consisting of the 16 (+/-4) kDa antigen and the 30 (+/-4) kDa antigen;

(Support for this is found at page 5, lines 13-24; page 7, lines 21-30; page 10, lines 30-34; page 12, lines 31-35; page 15, lines 18-21; page 26, lines 20-26; Example 1 at page 33, lines 25-34 of the specification; Example 3 illustrates a method for the isolation, excystation and culture of *Sarcocystis neurona*; page 19, line 2 through page 23, line 6 of the specification teach a variety of examples of methods which can be used to prepare the antigens.)

(b) admixing the antigen with an adjuvant to produce an admixture;

(Support for this is found at page 26, lines 27 through page 27, line 3; page 34, lines 7-10 of the specification.)

(c) immunizing a mammal with the admixture to produce antibodies against antigen;

(Support for this is found at page 34, lines 7-10 of the specification.)

(d) removing serum from the immunized mammal and isolating from the serum the antibody against the *Sarcocystis neurona* antigen selected from the group consisting of the 16 kDa +/-4 antigen and the 30 kDa +/-4 antigen; and

(Support for this is found at page 34, lines 12-14 of the specification)

(e) providing the isolated antibodies to the 16 and 30 kDa antigen together as the passive immunity vaccine in horses.

(Support for this is found at page 5, lines 13-24.)

(6) Grounds of Rejection to Be Reviewed on Appeal

(a) Claim 29 was rejected under 35 U.S.C. §103(a) as being unpatentable over Liang *et al.* 1998 (*Infection and Immunity;* 66(5) 1834-1838) and Marsh *et al.* 1996 (*JAVMA,* 209: 1907-1913) in view of Prescott *et al.* (*AJVR* 1997, 58: 356-359) and Higuchi *et al.* 1999 (*Journal of Veterinary Medicine* 46, 641-648).

(7) Argument

A. The Examiner rejected Claims 29 under 35 U.S.C. §103(a) as being unpatentable over Liang *et al.* 1998 (*Infection and Immunity;* 66(5) 1834-1838) and Marsh *et al.* 1996 (*JAVMA,* 209: 1907-1913) in view of Prescott *et al.* (*AJVR* 1997, 58: 356-359) and Higuchi *et al.* 1999 (*Journal of Veterinary Medicine* 46, 641-648).

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The cited prior art references do not teach or suggest all of the limitations of the claimed method. The cited references would not teach or suggest to a person of ordinary skill in the art a method for producing a passive immunity vaccine in horses with isolated antibodies to the 16 (+/-4) kDa antigen and the 30

(+/-4) kDa antigen of *Sarcocystis neurona* together. In addition, a prior art reference must be considered in its entirety, *i.e.*, as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), *cert. denied*, 469 U.S. 851 (1984). Therefore, it is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983). Liang *et al.* teaches away from a passive immunity vaccine with isolated antibodies to the 16 (+/-4) kDa antigen and the 30 (+/-4) kDa antigen of *Sarcocystis neurona* together.

Liang *et al.* teaches that serum and cerebrospinal fluid (CSF) from horses with a clinical diagnosis of a neurologic disorder resembling equine protozoal myeloencephalitis (EPM) reacted with combinations of Sn30, Sn16, Sn14, and Sn11 proteins from *Sarcocystis neurona* (*S neurona*) to form various band patterns on an immunoblot. The serum and CSF samples were grouped together by Liang *et al.* based upon the resulting band patterns. Liang *et al.* then teaches that *in vitro* neutralization assays against

Sarcocystis neurona merozoites isolated from bovine turbinate cell culture revealed "significant differences in inhibitory activities between the groups of serum and CSF samples with different immunoblot band patterns" (Liang *et al.*: page 1837, first full paragraph.) However, when Liang *et al.* correlated band patterns with inhibitory activities it was concluded that "no inhibitory activity correlating with antibody to Sn30 was noted." (Liang *et al.*: page 1836, first paragraph.) This can be clearly seen with sample N6 which recognizes the Sn30 protein of *Sarcocystis neurona.* (Liang *et al.*: Figure 2 on page 1836.) The teaching of Liang *et al.* therefore, would not show or suggest to a person of ordinary skill in the art that a passive immunity vaccine in horses with isolated antibodies to the 16 (+/-4) kDa antigen and the 30 (+/-4) kDa antigen of *Sarcocystis neurona* together should be pursued. A person of ordinary skill in the art would not be motivated to pursue the claimed method for producing the passive immunity vaccine after reading Liang *et al.* Liang *et al.* would actually lead a person of ordinary skill in the art away from the claimed invention, since *in vitro* neutralization assays against *Sarcocystis neurona* merozoites show that the Sn30 antigen

provides no inhibitory activity.

Marsh *et al.* 1996 does not add anything to the teachings of Liang *et al.* which would lead a person of ordinary skill in the art to the claimed invention. Marsh *et al.*, like Liang *et al.*, teach that serum and CSF samples from *Sarcocystis neurona* infected horses react with a protein band from *Sarcocystis neurona* merozoites of approximately 29 kDa. Marsh *et al.* further teaches that serum and CSF from a *Neospora* infected horse also apparently reacted with the 29 kDa protein band from *Sarcocystis neurona* merozoites. According to Marsh *et al.*, "the serologic evidence from the commercial laboratory's western blot test and results from the author's laboratory would indicate that the horse was coinfected with *Neospora* and *S neurona* or that antibodies produced from the *Neospora* infection cross-reacted to *S neurona* parasite antigens" (Marsh *et al.*: page 1911, right column, first full paragraph). Marsh *et al.* teaches that horses infected with *Neospora* can have antibodies which cross-react with this antigen so as to "have a false-positive reaction on the western blot assay for *S. neurona*, but that *Neospora*-infected horses can be specifically identified when they

also are tested for reactivity to *Neospora* antigens" (Marsh *et al.*: page 1911, right column at end of first full paragraph). This teaching by Marsh *et al.* would lead a person of ordinary skill in the art away from using the 30 kDa antigen from *Sarcocystis neurona* merozoites in a diagnostic test. Marsh *et al.* does not suggest to a person of ordinary skill in the art that a specific antibody to the 30 kDa antigen of *Sarcocystis neurona* is needed. The teachings of Marsh *et al.* only suggest that antibodies in the serum and CSF of *Neospora*-infected horses can cross-react with the 30 kDa antigen of *Sarcocystis neurona* in diagnostic tests. A person of ordinary skill in the art would in no way be motivated by Marsh *et al.* to produce an antibody to the 30 kDa antigen of *Sarcocystis neurona* for use as a passive immunity vaccine in horses by this teaching, alone or in combination with any of the other cited references.

Marsh *et al.* teaches "that *Neospora* sp should be considered in the differential diagnosis of EPM" (Marsh *et al.*: page 1912, left column, fourth full paragraph). This teaching of Marsh *et al.* would not motivate one of ordinary skill in the art to produce an antibody against the 30 kDa

antigen of *S. neurona* even for diagnostic purposes. According to Marsh *et al.* "pathologists need to be aware of morphologic differences in infections caused by *S. neurona* and *Neospora* sp. to avoid misdiagnosis." Marsh *et al.* conclude that there is a need for "confirmation of etiologic agents by use of immunohistochemical analysis, even when western blot results are positive for *S. neurona* antibodies (Marsh *et al.*: page 1912, right column, first paragraph). Marsh *et al.* base this conclusion on their own study, where they found tissue cysts in a *Neospora* infected horse which were "typical of *Sarcocystis* sp." (Marsh *et al.*: page 1912, left column, second full paragraph). Upon immunohistochemical staining of the tissue cysts, however, the cysts had a strongly positive reaction with polyclonal antiserum developed against the bovine *Neospora* sp tachyzoites, but the cysts did not react with the *S. neurona* antiserum. (Marsh *et al.*: page 1908, right column, first full paragraph; and Figure 2). Nothing about this approach for the confirmation of the etiologic agents by use of immunohistochemical analysis would lead a person of ordinary skill in the art to the claimed method for producing an antibody against the 16 kDa and 30 kDa antigens of

Sarcocystis neurona. Clearly, the *Neospora* sp antiserum and the *S. neurona* polyclonal antiserum were both used successfully to confirm the etiologic agent. Nothing would lead a person of ordinary skill in the art to isolate antibodies against specific 16 kDa and 30 kDa antigens of *Sarcocystis neurona* from the *S. neurona* polyclonal serum for even diagnostic purposes.

Prescott *et al.* teach passive immunization of foals against *Rhodococcus equi* pneumonia using plasma from a horse vaccinated with an acetone-precipitated, Triton X-extracted (APTX) antigen extracted from *R equi* with a high proportion of virulence-associated protein (VapA). Prescott *et al.* provide plasma for passive immunization, but Prescott *et al.* do not provide an antibody which has been isolated from the plasma as in the passive immunity vaccine of the claimed method. Prescott *et al.* teach that passive immunization with plasma from a vaccinated horse "appeared to enhance clearance of *R. equi* from the lungs of foals." (Prescott *et al.*: "Conclusions" on page 356, left column). However, Prescott *et al.* arrived at this conclusion "with considerable reservation because the number of foals used was low and 1 foal administered adult plasma without APTX

antibodies, but with a low residual titer of 10, cleared infection as well as did foals administered hyperimmune plasma." (Prescott *et al.*: page 358, first paragraph in right column). When the lung clearance in this foal was included with that in the other two foals given APTX antibody-negative plasma "there was no significant difference between this group and the group of foals given immune plasma." (Prescott *et al.*: "Passive immunization of foals against experimentally induced infection," page 357, right column). Therefore, a person of ordinary skill in the art would not likely pursue a passive immunity vaccine against *S. neurona* in horses after reading Prescott *et al.*

A person of ordinary skill in the art, after further reading of Prescott *et al.*, would question whether bacterial clearance data necessarily correlates with protection against *R. equi* pneumonia. Prescott *et al.* teach that *R. equi* is a cause of chronic pyogranulomatous pneumonia and lung abscesses in foals. (Prescott *et al.*: First paragraph on page 356, left column). Prescott *et al.* monitored lung clearance of bacteria to assess the effect of vaccination, because "despite heavy challenge exposure, pneumonic changes were not induced in any foal." (Prescott

et al.: "Discussion," page 358, right column). Prescott *et al.* further teaches that when foals are vaccinated with the APTX antigen in "contrast to the nonvaccinated foals, 4 of 8 vaccinated foals developed culture-confirmed *R. equi* pneumonia at 5 to 7 weeks of age." (Prescott *et al.*: page 358, first paragraph). Prescott *et al.* concludes that "paradoxically, vaccination of mares and their foals with APTX antigen did not protect foals and may have enhanced *R. equi* pneumonia in the foals." (Prescott *et al.*: "Conclusions" on page 356, left column). "At the time of development of pneumonia, these foals had a median serum ELISA titer of 2,560." (Prescott *et al.*: page 358, first paragraph). Since the IgG-ELISA containing the APTX antigen will detect IgG antibodies against the APTX antigen in the serum samples, a person of ordinary skill in the art would likely question whether boosting antibodies against specific antigens in horses would be useful for protecting against conditions such as *R. equi* pneumonia. (Prescott *et al.*: page 357, first paragraph). A person of ordinary skill in the art would therefore not be motivated to pursue a passive immunity vaccine in horses after reading Prescott *et al.*

Higuchi *et al.* teach passive immunization of foals

against *Rhodococcus equi* infection using hyperimmune plasma, but Higuchi *et al.* do not provide antibody which has been isolated from the plasma as in the passive immunity vaccine of the claimed method. While Higuchi *et al.* noted differences between foals receiving hyperimmune plasma and foals not receiving any plasma which suggest protection, "the differences observed were not statistically significant between the two groups of foals, those given hyperimmune plasma (1/16) and those not given hyperimmune plasma (5/19)." (Higuchi *et al.*: page 645, second full paragraph). Additionally, while the administration of hyperimmune plasma to foals maintained their ELISA antibody titres against *Rhodococcus equi* antigens to the established infection level, "other factors such as fibronectin, complement and cytokines in the hyperimmune plasma might also play a role." (Higuchi *et al.*: page 647, first paragraph). Therefore, Higuchi *et al.* do not suggest to one of ordinary skill in the art to isolate antibodies from the plasma to use as the passive immunity vaccine as in the claimed method.

Neither Prescott *et al.* or Higuchi *et al.*, either taken alone or in combination, would suggest to a person of ordinary skill in the art a method which provides isolated

antibodies as a passive immunity vaccine against *Sarcocystis neurona* in horses. Neither reference would convince a person of ordinary skill in the art that hyperimmune plasma as a passive vaccine protects against organisms such as the bacteria *Rhodococcus equi*. Neither reference even suggests a method for producing a passive immunity vaccine against the apicomplexan parasite *Sarcocystis neurona*. Liang *et al.* and Marsh *et al.* either taken alone or in combination, would not show or suggest to a person of ordinary skill in the art a method which provides isolated antibodies against the 16 and 30 kDa antigen together as the passive immunity vaccine in horses. Liang *et al.* actually teaches away from a method for producing a passive immunity vaccine which provides isolated antibodies against the 16 and 30 kDa antigen together. Therefore, the cited references would not lead a person of ordinary skill in the art to the claimed method.

B. Conclusion

As shown above, the claimed method is not obvious over the cited prior art references. Therefore, Claim 29 is patentable. Reversal of the Final Rejection is requested.

Respectfully,

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CLAIMS APPENDIX

29. A method for producing an antibody for use as a passive immunity vaccine in horses against a *Sarcocystis neurona* antigen selected from the group consisting of a 16 (+/-4) kDa antigen and a 30 (+/-4) kDa antigen, as determined by SDS polyacrylamide gel electrophoresis, comprising:

(a) providing a *Sarcocystis neurona* antigen selected from the group consisting of the 16 (+/-4) kDa antigen and the 30 (+/-4) kDa antigen;

(b) admixing the antigen with an adjuvant to produce an admixture;

(c) immunizing a mammal with the admixture to produce antibodies against antigen;

(d) removing serum from the immunized mammal and isolating from the serum the antibody against the *Sarcocystis neurona* antigen selected from the group consisting of the 16 kDa +/-4 antigen and the 30 kDa +/-4 antigen; and

(e) providing the isolated antibodies to the 16 and 30 kDa antigen together as the passive immunity vaccine in horses.